REMARKS

Status Summary

According to the United States Patent and Trademark Office (hereinafter the "Patent Office"), the instant application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). The current amendment provides the Abstract, which is identical to that presented on the cover page of PCT International Application WO 99/27963 from which the instant application is derived, with the exception of a deletion of one copy of an inadvertently repeated phrase ("antibody-producing cells") in the final sentence.

Claims 2 and 29-30 are pending in the subject application.

Claim 2 is currently canceled.

Claims 29-30 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Engle *et al.* (3 Immunity 39-50, 1995; hereinafter "Engle") in view of Nielsen *et al.* (2 EMBO J 115-19, 1983; hereinafter "Nielsen").

Claim 29 has been amended to recite that the monoclonal antibodies produced using the claimed method have a diverse repertoire of V_H and V_L rearrangements. Support for the amendment can be found throughout the specification of the application as filed, including particularly at page 49, lines 21-25; page 59, line 32, through page 60, line 3; and Example 4.

Claims 31 and 32 have been added. Support for the new claims can be found throughout the specification of the application as filed, including for claim 31 particularly at page 58, line 9, and Table 3; and particularly at page 9, line 31 through page 10, line 7, and page 62, line 11, through page 63, line 2 (autoantibodies); at page 10, lines 12-20, and page 14, lines 11-21 (highly conserved antigens) for claim 32.

No new matter has been introduced by any of the amendments. Favorable reconsideration is respectfully requested in view of the Amendments and Remarks.

Rejection of Claims 29-30 Under 35 U.S.C. § 103(a)

Claims 29 and 30 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Engle in view of Nielsen. According to the Patent Office:

> Engle teach immunizing CD19 transgenic mice overexpressing CD19 with an antigen. They teach that hCD19 transgenic mice had an overall increase in serum immunoglobulin levels. They go on to teach that overexpression of CD19 appears to render B cells more susceptible to differentiation induction. The data in table 2 show that the levels of isotype IgG2a and IgG2b antibodies are particularly higher in the hCD19 transgenic mice compared to wild type controls.

Official Action at pages 3-4.

However, the Patent Office concedes that Engle does not teach the process recited in steps (b) to (e) of claim 29 or specific affinity constants of the antibodies. According to the Patent Office, this defect is cured by Nielsen, which is asserted to teach a method of making monoclonal antibodies to an antigen and obtaining antibodies having an affinity constant of greater than 1×10^5 L/mol.

After careful consideration of the rejection and the Patent Office's basis for the rejection, applicant respectfully traverses the rejection and submits the following.

Applicant respectfully submits that according to the Patent Office assertions summarized above, Engle teaches the use of CD19 transgenic mice to quantitatively influence the antibody response of a mouse. CD19 transgenic mice are asserted to have increased serum immunoglobulin levels, increased susceptibility to differentiation induction, and higher IgG2 and IgG2b levels. In combination with Nielsen, the Patent Office asserts that it would have been prima facie obvious to one of ordinary skill in the art to substitute a wild type mouse with a CD19 transgenic mouse to produce monoclonal antibodies with a reasonable expectation of success. Thus, according to the Patent Office, "the ordinary skilled artisan would have been motivated to modify the claimed invention because CD19TG mice could produce higher levels of antibodies, particularly when the desired isotypes of the antibodies are IgG2a, 2b, and IgM". Official Action, at page 4.

Even assuming arguendo that the ordinary artisan would have been so motivated, applicant respectfully submits that, in contrast, the present application discloses and claims a qualitative difference between CD19 transgenic and wild type mice that is neither taught nor suggested by the Engle publication. Claim 29 recites that the monoclonal antibodies produced by the hybridoma are characterized by a

diverse repertoire of V_H and V_L rearrangements unlike that seen in wild type mice. As a consequence, whereas Engle might teach that CD19 transgenic mice produce more antibodies, the present application discloses and claims a method for producing an entirely unique and unexpected repertoire of antibodies from CD 19 transgenic mice.

The nature of this unexpected qualitative difference is discussed throughout the instant application as filed. For example, in Example 4, the immune response to a (4-hydroxy-3-nitrophenyl)acetyl (NP) hapten is described. As discussed in more detail in Example 4, C57BL/6 mice (the background strain for hCD19TG mice) normally produce an antibody response composed of antibodies containing a single V_H gene (V186.2) and λ1 light chains. CD19 transgenic mice, on the other hand, produced anti-NP antibodies that contained numerous unique V_H and V_L rearrangements, several of which had higher affinities for NP than antibodies formed in wild type mice. Additionally, none of the transgenic mice produced antibodies with the λ1 light chain. See Table 3 for additional characterization of the anti-NP response in transgenic mice.

Furthermore, applicant respectfully submits that Engle not only does not teach or suggest a qualitative difference between the antibody repertoires of transgenic and wild type mice, but it in fact teaches away from the concept that CD19 transgenic mice could be used for the generation of monoclonal antibodies to highly conserved and self-antigens. As is known in the art, animals do not normally produce antibody responses to highly conserved and self-antigens (the former often seen by the animals as essentially self antigens) because immature B cells that would otherwise produce such antibodies are subject to clonal deletion in the bone marrow that express high affinity IgM receptors that are reactive with self-antigens. According to Engle:

> The finding that overexpression of CD19 results in increased sensitivity to transmembrane signals in combination with the finding that overexpression of CD19 results in clonal elimination of B cells in the bone marrow suggests that CD19 regulates antigen-dependent negative selection of immature B cells during maturation in the bone marrow. Since impaired B cell development in hCD19TG mice is directly correlated with the number of cell surface hCD19 molecules

> expressed...increased receptor number may translate into the overproduction of intracellular signals, which exceeds the signaling threshold and results in down-regulation of immature B cell development. Since many preimmune B cells produce self-reactive antibodies...lowering the surface immunoglobulin signaling threshold for negative selection by overexpressing CD19 may explain the severe deficiency of B cells in hCD19TG mice...Thus, overexpression of CD19 may augment transmembrane signals generated through low affinity antigen receptors, thereby leading to increased clonal deletion of immature B cells in the bone marrow"

Engle at page 47 (citations omitted).

Applicant respectfully submits that one of ordinary skill in the art would interpret the preceding to imply that CD19 transgenic mice would have a greatly reduced antibody repertoire, as a greater percentage of immature B cells are clonally eliminated in the bone marrow. Thus, based upon the teachings of Engle, CD19 transgenic mice would have been expected to be even less likely to produce antibodies to highly conserved and self-antigens.

However, in direct contrast to the teachings of Engle, the instant application discloses and claims a method for producing monoclonal antibodies characterized by a more diverse repertoire of V_H and V_L rearrangements than that seen in wild type mice (*i.e.* mice that express lower levels of CD19 than hCD19TG mice). Furthermore, the method can even be used to generate monoclonal antibodies to highly conserved and self-antigens, a fact that one of ordinary skill in the art would not possibly have been motivated to consider in light of the teachings of Engle. As a result, applicant respectfully submits that with knowledge of the teachings of Engle, one of ordinary skill in the art would not have been motivated or indeed even able to produce monoclonal antibodies with the diverse repertoire of rearrangements as claimed in the instant method with a reasonable expectation of success.

In view of the arguments presented herein above, applicant respectfully submits that the subject matter of the instant application has been patentably distinguished from the teachings of Engle in view of Nielsen. Accordingly, applicant respectfully requests that the rejection of claims 29 and 30 under 35 U.S.C. § 103(a) based upon these references be withdrawn, and that the claims be allowed at this time.

New Claims

Claims 31-32 have been added. These claims recite a method for producing a monoclonal antibody wherein said monoclonal antibodies characterized by the presence of two (2) or fewer somatic mutations in a V_H region (claim 31, and a method for producing a monoclonal antibody specific for an antigen, wherein the antigen is selected from the group consisting of an autoantigen and a highly conserved antigen (claim 32). Support for the new claims can be found throughout the specification of the application as filed, including for claim 31 particularly at page 58, line 9, and Table 3; and particularly at page 9, line 31 through page 10, line 7, and page 62, line 11, through page 63, line 2 (autoantibodies); at page 10, lines 12-20, and page 14, lines 11-21 (highly conserved antigens) for claim 32. Allowance of claims 31 and 32 is respectfully requested.

CONCLUSIONS

In light of the above remarks and the cancellation of all non-allowed claims, applicant submits that the subject patent application is in condition for allowance and such allowance is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to place the application in condition for allowance.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: August 13, 2003 By: Arles A. Taylor, Jr.

Arles A. Taylor, Jr.
Reg. No. 39,395

180/95 PCT/US AAT/CPP/ptw

Customer No. 25297

OFFICIAL